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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/156,367	09/17/98	LIU Y	YFL98-01PA

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EXAMINER	
ALLEN, M	
ART UNIT	**PAPER NUMBER**
1631	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/156,367	Applicant(s) LIU, YA FANG	
	Examiner Marianne P. Allen	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2000 and 08 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21-24,27-31,44 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21-24,27-31,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Claims 20, 25, and 32 have been cancelled and claim 45 has been newly added. Claims 1-19, 21-24, 27-31, and 44-45 are under consideration by the examiner.

Applicant's arguments filed 12/14/00 and 2/8/01 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant is being given benefit to the instant filing date (9/17/98) and being denied benefit to the provisional application filing date (5/14/98). As presently written, the full scope embraced by each claim was not disclosed in the provisional application. The methods as claimed were not disclosed in the provisional application. The provisional application is essentially a research paper and discloses particular experiments performed. There is no generic disclosure of the methods as presently claimed. Applicant's arguments are unpersuasive with respect to support for the claimed invention in the provisional application. None of the claims is limited to the material disclosed in the provisional application. All of the claims embrace broader concepts. In any event, note that the prior art applied below antedates applicant's asserted priority claim.

Claims 1-6, 9-11, 14-21, and 44-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the methods exemplified in the specification, does not reasonably provide enablement for the breadth of the claims as set forth below. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification states on page 10 that MLK1, MLK2, and MLK3 are the only kinases known to directly activate the SEK1-JNK cascade and that MLK2 is the neuronal form. For those claims not limited to MLK1, MLK2, and MLK3 other MLK's are not enabled essentially for reasons of record. While applicant has argued on page 8 of the 12/4/00 response that kinases with certain structural and functional limitations would not constitute undue experimentation to determine thereby enabling other MLK's within the claims, this is not persuasive. The structural features listed in the response for such MLK's are not limitations of the claims. The functional limitations introduced into the claims remain broad (i.e. unspecified "enzymatic activity"). Note that the specification identifies only kinase enzymatic activity associated with MLK's and no others. It is noted that there is no requirement in the claims for direct phosphorylation of SEK1 protein. As the SEK1 protein is part of a large cascade of kinase activated proteins, the proteins embraced by the claims remains large.

In addition, the specification fails to disclose any mutated proteins other than polyglutamine stretch-expanded huntingtin or C-terminal 100 amino acids of amyloid precursor that would induce apoptosis in neuronal cells. See at least claims 2 and 9. It is deemed to constitute undue experimentation to determine other mutated proteins that would cause apoptosis in neuronal cells and in association with MLK's in the absence of further guidance.

Claims 7-8, 12-14, 22-23, 28, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7-8, 12-13, and 22-23 are confusing in depending upon claims which do not exist. Note that there are no claims 46, 47, or 51 pending in the instant application.

Claim 14 is confusing in reciting "potentially useful drug for treating the mammal" in the body of the claim. Neither the preamble nor method steps are directed to mammals.

Claim 28 does not appear to further limit the subject matter of claim 27 as the SEK1 and phosphate donor would appear to be implicit by the limitations of claim 27 for phosphorylated SEK1.

Claim 31 is confusing in reciting "cell viability status" as this limitation is not present in claim 29 upon which it depends.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-2, 6, 9, 14, 19, 21, 24, 28-31, and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Miller et al. (U.S. Patent No. 6,060,247).

Miller et al. discloses and claims methods of identifying substances that inhibit apoptosis in postmitotic neurons by culturing postmitotic neurons, infecting them with adenovirus vectors comprising DNA encoding a protein that causes apoptosis, exposing the neurons to the test substance, and determining the number of neurons that undergo apoptosis compared to a control. (See claim 28.) One of the adenoviral vectors exemplified uses MEKK1 which induces apoptosis. (See Figure 11 and column 24.) MEKK1 would have been known to phosphorylate SEK1. (See for example Yan et al., Nature, 372:798-800, 1994.) As such the infected neuronal cells of Miller et al. appear to meet the limitation in the claims of "neuronal cells having activated MLK activity, wherein the activity is selected from the group consisting of an enzymatic activity, an ability to bind a SEK1 protein, and an ability to phosphorylate a SEK1 protein." Neuronal cells expressing MEKK1 would have phosphorylated SEK1. Determining protein phosphorylation levels is disclosed at least at column 3, last paragraph. With respect to claims 19, 21, 24, and 45, Miller et al. also specifically discloses using adenoviral vectors expressing mixed lineage kinases SPRK (the instant MLK3) and DLK (the instant MLK2) in the assays. (See column 29, lines 53-55.) These would have been known to phosphorylate SEK1 as acknowledged by the specification and prior art of record. With respect to the claim limitation "expressing a mutated protein" (for example, claim 2), Miller et al. discloses that full length proteins or fragments encoding biologically active proteins may be used. (See column 2, line 49-50.) With respect to the claim limitation "apoptotic neuron" (for example, claim 6), the neurons of Miller et al. undergo apoptosis and thus meet this limitation. With respect to claim 14, the infected neurons of Miller et al. would be surviving cells

implicitly contacted with the agent that causes apoptosis when contacted with the test substance. With respect to claim 30, Miller et al. discloses cell viability assays in apoptosis at column 14, line 50, through column 15, line 20.

Claims 19,21, 24, and 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Tibbles et al., Rana et al. (Ref. AY3), and Hirai et al. (Ref. AS3) each in view of Au-Young et al. (U.S. Patent No. 5,817,479).

Au-Young et al. discloses the desirability of identifying inhibitors of kinases. (See abstract, column 5, lines 14-20, and columns 23-24.) The MAP kinase family and in particular c-Jun cascade are disclosed. (See columns 3-4.) MLK2 is disclosed in Table 1 at column 26. The reference does not disclose MLK1 or MLK 3 nor the association of MLK1, MLK2, and MLK3 with SEK1.

Rana et al. discloses that MLK1 directly phosphorylated SEK1. Hirai et al. discloses that MLK2 directly phosphorylated SEK1. Tibbles et al. discloses that MLK3 directly phosphorylates SEK1. None of the references specifically discloses finding direct inhibitors of MLK1, MLK2, or MLK3 activity, particularly with reference to SEK1.

It would have been obvious to take the MLK1 protein of Rana et al. or the MLK2 protein of Hirai et al. or the MLK3 protein of Tibbles et al. and screen for direct inhibitors such that SEK1 phosphorylation did not occur. One would have been motivated to do so in view of the desirability of such inhibitors as taught by Au-Young et al. One of ordinary skill in the art would

have known that SEK1 was a substrate for these MLK kinases as evidenced by Rana et al., Hirai et al., and Tibbles et al. references. It would have been well known and routine to perform such kinase inhibition assays at the time of the invention.

This action is being made non-final. Even though applicant has substantively amended the claims, it appears that the prior art applied herein should reasonably have been identified and applied against some of the prior claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen, whose telephone number is (703) 308-0666. The examiner can normally be reached on Monday-Friday from 9:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028. Official FAX communications may be directed to either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning the formalities of this application should be directed to Patent Analyst Tina Plunkett whose telephone number is (703) 308-0009.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER
~~GROUP 1600~~
Au1631